

BMJ Open Effect of using cardiovascular risk scoring in routine risk assessment in primary prevention of cardiovascular disease: protocol for an overview of systematic reviews

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ABSTRACT

Introduction: Major clinical practice guidelines recommend assessing risk of cardiovascular disease (CVD) using absolute/global/total CVD risk scores. However, the effectiveness of using them in clinical practice, despite publication of numerous randomised controlled trials (RCTs), is still poorly understood. To summarise and analyse current knowledge in this field, we will carry out an overview of existing systematic reviews (SRs). The objective of this overview will be to assess the effect of using cardiovascular risk scoring in routine risk assessment in primary prevention of CVD compared with standard care.

Methods and analysis: We will include SRs and meta-analyses which take into account RCTs and quasi-RCTs investigating the effect of using cardiovascular risk scoring in routine risk assessment in primary prevention of CVD. SRs will be retrieved from 4 bibliographical databases and reference lists of identified reviews. Additionally, the PROSPERO database will be searched for unpublished, ongoing or recently completed SRs. 2 reviewers will assess the SRs independently for eligibility and bias. The data will be extracted to a special form. Any disagreement will be resolved by discussion. In case of lack of consensus, a third author will arbitrate. The overview of SRs will be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement.

Ethics and dissemination: Ethics approval is not required for overview of SRs. We will summarise evidence concerning whether use of the absolute/global/total CVD risk scoring tools in primary prevention of CVD is effective and supported with scientific data or not. If we face unsatisfactory confirmation, we will highlight a need for further research and advice on how to plan such a study. We will submit the results of our study for peer-review publication in a journal indexed in the international bibliographic database of biomedical information.

Strengths and limitations of this study

- We anticipate our study to be the first and largest overview of systematic reviews in this area.
- A robust search strategy has been prepared by an experienced librarian.
- Electronic search strategy is limited to four main international bibliographic databases and the English language literature only.
- This article is a protocol of the overview of systematic reviews. The results of the overview will be published in a different article.

INTRODUCTION

Cardiovascular disease (CVD) is nowadays the leading cause of mortality, morbidity and disability worldwide.^{1 2} Well-established, modifiable CVD risk factors are: elevated blood pressure, hypercholesterolaemia, diabetes, obesity, lack of physical activity, inappropriate diet, excessive alcohol intake and smoking. Understanding CVD risk factors makes prevention possible. Risk factor modification can reduce the number of premature deaths as well as other clinical events, both in people with confirmed CVD (secondary prevention) and people without established CVD, who are at high cardiovascular (CV) risk (primary prevention).

The Framingham Heart Study was the first well-constructed observational study to investigate CV risk factors.³ The first major findings were reported in 1957,⁴ and it was shown that hypertension (HTN) increases coronary heart disease (CHD) incidence. The breakthrough in understanding CHD risk came with an article by Kannel *et al*⁵ in 1961, when the term ‘factors of risk’ was

used and it was proved that HTN, hypercholesterolaemia and other risk factors 'precede the development of overt CHD in humans and are associated with increased risk of development of CHD'.

After individual risk factors of CVD were identified in the Framingham Heart Study,³ the new concept of the absolute/global/total CVD risk was taken into consideration. By definition, absolute CVD risk is the actual risk of developing this disease by the defined population in a defined period of time (mostly 10 or 5 years).⁶ The absolute/global/total CVD risk is calculated by using a combination of present major risk factors. To individualise the absolute/global/total risk for an individual patient, risk scores, which use function equations based on multiple risk factors, are in use.⁷

The first multivariate analysis on the Framingham Cohort was published by Truett *et al*⁸ in 1967.

After the success of the Framingham Heart Study, other risk scores were created in the USA, European countries and other parts the world, and their numbers grew rapidly. In 2008, Beswick *et al*⁹ identified 110 prognostic models or risk scoring methods with potential use in targeting primary prevention of CVD. The most well-known and widely used are: Systematic COronary Risk Evaluation (SCORE) algorithm,¹⁰ QRISK¹¹ and QRISK2,¹² the WHO risk score, and American College of Cardiology/American Heart Association (ACC/AHA) 2013 Pooled Cohort risk equations.¹³

A research project for the development of the European CVD risk-prediction model (SCORE project) was initiated by the Working Group on Epidemiology and Prevention of the European Society of Cardiology (ESC) in 1994. To ensure best applicability in the European region, the SCORE project gathered a pool of data sets from 12 European cohort studies. The SCORE model predicts the 10-year risk of CV mortality in individuals (aged 40–65) without pre-existing CVD. The total CVD risk is calculated using individual's gender, smoking status, age, blood pressure and total cholesterol level (or total cholesterol/high-density lipoprotein cholesterol ratio).¹⁰ Since its publication date, many countries have developed specific versions of the SCORE.^{14–17}

Major clinical practice guidelines (Canadian Cardiovascular Society (CCS),¹⁸ European Society of Cardiology/European Society of Hypertension (ESC/ESH),¹⁹ ACC/AHA,²⁰ Joint British Societies (JBS3)²¹) recommend assessing risk of CVD using the absolute/global/total CVD risk scores. It was confirmed that use of risk scores increases the accuracy of prediction of CVD events and may guide management decisions in primary prevention. Unfortunately, only a few global CVD risk scores were externally validated. Validation is an important feature which is used to evaluate the performance of risk score models and to verify, whether they can be applied outside the settings in which they were developed.

The effectiveness of using absolute/global/total risk scores can be proved by randomised control trials (RCTs). Some RCTs were published over the past two

decades. The research community tried to summarise existing evidence in this field, which resulted in the publication of a few systematic reviews (SRs).

In 2006, Brindle *et al*²² published a well-known work in which they tried to assess the impact of CVD risk prediction on clinical outcomes. However, they did not find a strong correlation. Since then, several papers have been published^{23–25} with similar conclusions. Moreover, in 2015, two SR protocols focusing on the influence of using CVD risk scoring on care and outcomes were published. The first, by Karmali *et al*²⁶ was published in the Cochrane Library. The second, by Tomasik *et al*,²⁷ is available online.

Despite numerous publications, there are still unsolved issues. One of them is whether using the absolute/global/total CVD risk scoring (total risk assessment—TRA) is clinically effective when outcomes important for patients are taken into account (eg, mortality, CV events). Additionally, there are not much data about the adverse effects of TRA. The absence of information does not mean that the procedure is completely safe.

Even though, TRA for CVD has high external validity since it appropriately predicts CV events, it does not mean that beneficial clinical effects will be obtained when using it.

The first and main barrier limiting the knowledge in this area is, in fact, that there were only a few experimental studies measuring the efficacy of using TRA tools. On the contrary, however, quite a lot of studies referring to calibration and discrimination were published. The second barrier is that in some studies the surrogate end points were used to show effectiveness. In the literature we may find examples which demonstrate a benefit from a particular intervention when surrogate markers were used, but later, a repeated study regarding hard outcomes did not demonstrate a benefit or even showed harm.²⁸

In this connection, the effectiveness of using global CVD risk scores in clinical practice is still poorly understood. On the one hand it can be beneficial and improve health (eg, identifying high-risk individuals who will most likely benefit from risk factor management). On the other hand, it may be harmful (undertreatment of youngsters or overtreatment of the elderly) and misuse resources (eg, time and cost of laboratory tests).

Objectives

We will carry out an overview of existing SRs. Such an overview is suggested as a logical and appropriate step for comparing and contrasting separate reviews. Our objectives in this study are: (1) to analyse and summarise the best current evidence for the effectiveness of using CV risk scoring in routine risk assessment in primary prevention of CVDs compared with standard care; (2) to assess whether use of a particular risk score followed by structured or unstructured intervention is more effective than another risk score in improving patient outcomes; and (3) to discuss how our findings can be used to

guide clinicians, policymakers and provide a guideline for authors in future.

METHODS/DESIGN

Our research methods will follow the 'Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols' (PRISMA-P).^{29 30} The PRISMA-P checklist is presented in an online supplementary appendix 1.

Eligibility criteria

Studies will be selected according to the criteria defined below.

Studies

We will include SRs and meta-analyses which take into account RCTs and quasi-RCTs investigating the effect of using CV risk scoring in routine risk assessment in primary prevention of CVD. If SRs also take into account other studies (ie, observational), they will be included as well. We will include both SRs reported as full text as well as any published as abstract only. Included reviews have to describe a systematic search strategy.

Participants

Participants will be adults (19 years of age and over) free of clinical CVD. They may have different CVD risk factors or other diseases including diabetes and chronic kidney disease.

Interventions

Intervention: CVD risk assessment with use of the absolute/global/total CVD risk scoring (TRA), performed by physicians or other healthcare professionals.

Comparator: Standard care with no use of the global CVD risk scoring provided by a physician or healthcare professional. Treatment and lifestyle recommendations in comparative intervention should be based on other methods, for example, assessment of only one particular risk factor, counting the number of risk factors or no CVD risk assessment at all (treatment based completely on physicians' 'gut feeling').

Outcomes

Primary outcomes: (1) CVD death, (2) fatal and non-fatal CV event, (3) adverse events—(any physical, psychological or social events).

Secondary outcomes: (1) All-cause mortality, (2) change in predicted global CVD risk, (3) change in patient CVD risk factors—change in blood pressure, cholesterol level, smoking, exercise, diet, alcohol consumption and obesity, (4) prescription of risk-reducing drugs according to prevailing guidelines (aspirin, antihypertensives, lipid-lowering agents), (5) pharmacotherapy without or against current clinical guideline recommendations.

Adverse events mentioned as primary outcomes could be as follows: (1) physical—for example, HTN or

dyslipidaemia complications in young patients who were excluded from pharmacotherapy due to low CVD risk score; (2) psychological—for example, anxiety, depression, stress caused by diagnosis and being labelled as 'chronically ill'; (3) social—for example, costs and additional time spent on unnecessary consultations, roles changing in family or society.

Setting

Only studies performed in a primary care setting will be eligible.

Information sources

We will identify SRs through systematic searches of the following databases:

- ▶ MEDLINE (Ovid);
- ▶ EMBASE;
- ▶ CENTRAL (Cochrane Central Register of Controlled Trials);
- ▶ SCOPUS.

We will search all databases from 1990 to the present (only a very small number of SRs were conducted before that time).^{31 32} The search will be limited to the English language literature. This search will be supplemented by a search for unpublished, ongoing or recently completed SRs in PROSPERO. In addition, we will also hand search the reference lists of all included SRs.

Search strategy

The preliminary search strategy for MEDLINE (Ovid) is presented in online supplementary appendix 2. Search strategy was based on that presented in one of the authors' previous studies.²⁷ Search terms containing names of different CVD risk scores were adopted from the work of Beswick *et al.*⁹ Search strategy for MEDLINE will be adapted for use in other databases.

STUDY RECORDS

Data management

All records identified will be uploaded or manually entered into Mendeley V.1.16.3 (Elsevier).

Selection process

After initial duplicate removal, titles and abstracts from the searches will be independently screened by two authors (KS, JK). Full-text articles will be retrieved for all potentially includable SRs or SR protocols. Any disagreements will be resolved through discussion. In case of lack of consensus, a third author (TT) will arbitrate. If any ongoing or unpublished study is identified, we will contact the corresponding author for information about whether any preliminary data may be included in our overview.

Data collection process

The methodology for data extraction and analysis will be based on the guidance from Preferred Reporting Items

for Systematic Reviews and Meta-Analyses (PRISMA) statement³³ and the Cochrane Handbook of Systematic Reviews of Interventions.³⁴

Two authors (KS, JK) will independently extract outcome data from each included review using a predefined data extraction form. This form will be developed and will be piloted using the first three eligible reviews and amended where required. Disagreements during the data extraction process will be resolved through discussion. In case of lack of consensus, a third author (TT) will arbitrate.

Data items

We will extract the following information: (1) administrative and bibliographic data (author names and institutions, journal title, publication year, role of study sponsors and funding sources, reported conflicts of interest); (2) the characteristics of each review (primary research questions and all outcomes for which data were sought, eligibility criteria used, number and bibliographic data of primary studies included, the applied search strategy including search periods, study selection methods and applied limitations); (3) methodological details and results of meta-bias assessments (if conducted); (4) reported limitations of each review; (5) results and conclusions of the review.

Additionally, we will extract the following information: (1) outcomes reported in a particular SR, which were recognised by the authors as evidence of the effectiveness of TRA, (2) reported effect of TRA in different populations, and (3) reported effect of different TRA in the same population.

We will also describe how the fatal and non-fatal CV events were defined in each SR.

If a meta-analysis has been conducted, we will extract both its results and all relevant methodological aspects (eg, types and unity of data, effect measured, heterogeneity, sensitivity analysis).

Outcomes and prioritisation

All outcomes, for which data will be sought, are listed in the 'outcomes' subsection in the 'eligibility criteria' section of this protocol. We assume that primary outcomes chosen for this study are most important because: (1) they are objective and clinically relevant; and (2) they include beneficial and adverse effects. We would like to emphasise that in our study, adverse events are also considered as 'main' outcomes, because of their importance in everyday practice. Although secondary outcomes are less important, we are convinced that they will help to understand the influence and outcomes of using the absolute/global/total CVD risk scoring in general practice and give information for researchers planning further studies.

Risk of bias in included SRs

Currently there is no gold standard for the assessment of risk of bias for each SR included in an overview.^{34 35}

Two reviewers (KS, TT) will independently appraise risk of bias of the included SRs using validated AMSTAR (assessment of multiple SRs) checklist, which is most commonly used to assess the quality of SRs included in overviews.³⁵ We will score each SR with a maximum of 11 points. Disagreements will be resolved through discussion. In case of lack of consensus, a third author (JK) will arbitrate. Each SR will be assigned to one of three quality levels (0–3 points—low quality, 4–7 points—medium quality and 8–11 points—high quality).^{36 37}

DATA

Data synthesis

Presentation of results of our study will align guidelines from the PRISMA statement³³ and the Cochrane Handbook of Systematic Reviews of Interventions.³⁴ A PRISMA flow diagram will be used to summarise search results. Data will be presented as a narrative synthesis. A series of summary tables and figures will supplement textual commentary to enhance the clarity of our reporting.³⁸ We will also report outcomes of interest for which no reviews were found. We will not conduct a meta-analysis of meta-analyses. Even when two or more suitable meta-analyses are found, we do not plan to do that because of the risk of introducing bias. According to Smith *et al*³⁸ and Pieper *et al*³⁹ such undesired bias can be easily incorporated (due to giving excessive statistical power to primary studies included in more than one SR) when performing meta-analysis in review of SRs. Moreover, the same authors highlight that planning such meta-analysis requires careful consideration and there is no well-established quantification method in this field.

Risk of bias across SRs

To assess selective outcome reporting within SRs, we will compare outcomes which were planned to be assessed in the SR protocols (or, if unavailable, in the methods section of the published report of SR) and others reported in the results section of the published report of SR.

To minimise publication bias, we would like to identify all relevant unpublished or ongoing SRs by searching the PROSPERO database. If we succeed, we will contact the corresponding author and ask for preliminary data that can be included in our overview.

To assess the degree of overlap in the inclusion of primary studies between SRs, the citation matrix will be generated by one reviewer and checked by a second for accuracy. It will cross-link SRs (columns) with primary studies included in SRs (rows). The degree of overlap will be calculated with use of the corrected cover area in our citation matrix.³⁹

Confidence in cumulative evidence

To strengthen the body of evidence, in our overview we will take into account SRs analysing RCTs, quasi-RCTs and non-experimental prospective trials.

We will use the assessment of quality of evidence performed by original SR authors. We will appraise the quality of evidence across the domains of risk of bias, precision, consistency and publication bias.

DISCUSSION

Our review will be a comprehensive synthesis of the existing SR literature describing the effectiveness of using CV risk scoring in routine risk assessment in primary prevention of CVD. To the best of our knowledge, it will be the first such study in this area.

In the discussion section in the full report of our study, we plan to include the following subsections, typical for this type of study: (1) summary of main findings; (2) strength and limitations; (3) comparison with other studies and opinions; (4) interpretation of results; (5) ethical considerations and funding; and (6) conclusion.

We are aware that the methodology of overview of SRs is less developed than the methodology of SRs.

We strongly believe that results of our study will be important for medical professionals. They will receive up-to-date and persuasive evidence, whether use of the TRA tools in primary prevention of CVD is supported by scientific data or not. If the legitimacy of using TRA is proved then that will be additional encouragement for using this tool in everyday practice by healthcare professionals in future. Our best intention is also to provide sufficient data for policymakers, which will help them to project and conduct CVD primary prevention programmes in future. We are convinced that our study will be interesting for researchers. We suspect it will uncover gaps in our knowledge and therefore reveal areas of future research. We hope that the results of our study will improve (non-directly) the health of many patients. Receiving information about a strong scientific background of performed CVD risk assessment will boost patients' adherence to instructions from the physician on non-pharmacological or pharmacological therapy.

Contributors KS and TT conceived the study design. KS, TT, JK, JJ and AW contributed to developing the methods. KS, JK and TT developed the search strategy. JJ and AW provided methodological expertise. KS and TT drafted the protocol manuscript. KS, TT, JK, JJ and AW read, provided feedback on and approved the final manuscript.

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Competing interests TT reports personal fees from AbbVie Polska Sp. z o.o., personal fees from Pfizer Polska Sp. z o.o., non-financial support from VALEANT POLSKA sp. z o.o. sp. j., outside the submitted work. JJ reports personal fees from VALEANT personal fees from MYLAN, non-financial support from CHDE, non-financial support from AMGEN, outside the submitted work. AW reports personal fees from MSD Polska sp. z o.o., personal fees from Merck sp. z o.o., personal fees from Sanofi-Aventis sp. z o.o., personal fees from Polpharma SA, outside the submitted work.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The authors will submit the results of the study for peer-review publication in a journal indexed in the international bibliographic database of biomedical information.

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